

to the patient of a compound that selectively inhibits T<sub>ck</sub> cells.

57(New). A method according to claim 56 wherein said compound is a nucleic acid molecule encoding a polypeptide which selectively inhibits T<sub>ck</sub> cells.

58(New). A method according to claim 56 wherein said compound selectively inhibits T<sub>ck</sub> cell-induced release of one or more pro-inflammatory cytokines from monocytes.

59(New). A method according to claim 58 wherein the cytokine is tumour necrosis factor- $\alpha$ .

A3 60(New). A method according to any one of claims 56-59 wherein said compound selectively inhibits NF- $\kappa$ B.

61(New). A method according to any one of claim 56-59 wherein said compound selectively activates PI3 kinase.

62(New). A method according to claim 60 wherein the nucleic acid molecule encodes an NF- $\kappa$ B inhibitor, preferably I $\kappa$ B $\alpha$ .

63(New). A method according to claim 61 wherein the nucleic acid molecule encodes an NF- $\kappa$ B inhibitor, preferably I $\kappa$ B $\alpha$ .

64(New). A method of identifying a compound with efficacy in the treatment of a chronic inflammatory disease comprising the step of testing the compound for an ability to selectively inhibit T<sub>ck</sub> cells.

65(New). A method according to claim 64 wherein testing the compound for an ability to selectively inhibit T<sub>ck</sub> cells comprises testing the compound for an ability to selectively inhibit T<sub>ck</sub> cell-induced release of one or more pro-inflammatory cytokines from monocytes.

66(New). A method according to claim 65 wherein the cytokine is tumour necrosis factor- $\alpha$ .

67(New). A method according to claim 66 wherein said method comprises the following steps:

- A<sup>3</sup>
- (i) pre-incubating monocytes with a compound to be tested;
  - (ii) resuspending said pre-incubated monocytes in the absence of the test compound;
  - (iii) stimulating said resuspended monocytes by co-culturing with either T<sub>ck</sub> cells or T<sub>tcr</sub> cells; and
  - (iv) assaying for TNF $\alpha$  production by said stimulated monocytes.

68(New). A method according to claim 66 wherein said method comprises the following steps:

- (i) pre-incubating separate cultures of T<sub>ck</sub> cells and T<sub>tcr</sub> cells with a compound to be tested either prior to fixation or during their activation in culture;
- (ii) resuspending said T<sub>ck</sub> cells and T<sub>tcr</sub> cells in the absence of the test compound;

- (iii) stimulating monocytes by co-culturing with said resuspended  $T_{ck}$  cells or  $T_{tcr}$  cells; and
- (iv) assaying for  $TNF\alpha$  production by said stimulated monocytes.

69(New). A method according to any one of claims 64-68 wherein the chronic inflammatory disease is a disease of humans.

70(New). A method according to claim 69 wherein the chronic inflammatory disease is rheumatoid arthritis.

71(New). A method according to claim 64 wherein testing the compound for an ability to selectively inhibit  $T_{ck}$  cells or selectively inhibit  $T_{ck}$  cell-induced release of one or more pro-inflammatory cytokines from monocytes comprises determining whether the compound exhibits NF- $\kappa$ B inhibition.

72(New). A method according to claim 71 wherein NF- $\kappa$ B inhibition is constituted by a reduction in the binding of nuclear extracts, derived from monocytes exposed to the compound, to an NF- $\kappa$ B promoter DNA oligonucleotide.

73(New). A method according to claim 72 wherein a reduction in the binding of nuclear extracts, derived from monocytes exposed to the compound, to an NF- $\kappa$ B promoter DNA oligonucleotide is determined by an electrophoretic mobility shift assay (EMSA).

74(New). A method according to any one of claims 71-73 wherein NF- $\kappa$ B inhibition is deemed to exist if the binding of

A<sup>3</sup>

NF- $\kappa$ B to an NF- $\kappa$ B promoter DNA oligonucleotide is reduced to no more than 50%, a presumption being strengthened as that percentage approaches zero.

75(New). A method according to claim 71 wherein NF- $\kappa$ B inhibition is constituted by a reduction in expression of the NF- $\kappa$ B gene.

76(New). A method according to claim 75 wherein a reduction in the expression of the NF- $\kappa$ B gene is determined by a reporter gene assay.

A<sup>3</sup> 77(New). A method according to claim 76 wherein the reporter gene assay comprises coupling a  $\beta$ -galactosidase gene to the NF- $\kappa$ B gene and determining a reduction in  $\beta$ -galactosidase activity.

78(New). A method according to claim 77 wherein  $\beta$ -galactosidase activity is reduced to no more than 50%.

79(New). A method according to claim 64 wherein testing the compound for an ability to selectively target T<sub>ck</sub> cells or selectively inhibit T<sub>ck</sub> cell-induced release of one or more pro-inflammatory cytokines from monocytes comprises determining whether the compound exhibits PI3 kinase activation.

80(New). A method according to claim 79 wherein PI3 kinase activation is constituted by an increase in PI3 kinase activity in monocytes exposed by the compound.

81(New). A method according to claim 80 wherein PI3 kinase activation is deemed to exist if there is an increase in PI3 kinase activity equivalent to a range from at least 50% of the increase induced by IL-10 stimulation (100 ng/ml for 2 minutes), to an amount greater than the increase induced by IL-10 stimulation.

82(New). A compound identified as having efficacy in the treatment of a chronic inflammatory disease by testing the compound for an ability to selectively inhibit T<sub>ck</sub> cells or selectively inhibit T<sub>ck</sub> cell-induced release of one or more pro-inflammatory cytokines from monocytes.

83(New). An antibody-like molecule having specificity for T<sub>ck</sub> cells.

A<sup>3</sup> 84(New). An antibody-like molecule according to claim 83 selected from the group of molecules consisting of Fab molecules, F(ab<sup>1</sup>)<sub>2</sub> molecules, Fv molecules, disulphide-linked Fv molecules, single chain Fv (scFv) molecules and single domain antibodies (dAbs).

85(New). An antibody-like molecule according to claim 83 wherein said antibody-like molecule is humanized.

86(New). An antibody-like molecule according to claim 84 wherein said antibody-like molecule is humanized.

87(New). A method of making an antibody-like molecule having specificity for T<sub>ck</sub> cells.

88(New). An isolated cell that expresses an antibody-like molecule having a specificity for T<sub>ck</sub> cells.

89(New). An isolated cell according to claim 88 wherein the cell is a hybridoma cell.

90(New). A method for identifying an antibody-like molecule having specificity for T<sub>ck</sub> cells comprising the following steps:

- (i) providing a population of T<sub>ck</sub> cells; and
- (ii) using said T<sub>ck</sub> cells to screen a library of antibody-like molecules.

91(New). A method according to claim 90 wherein the antibody-like molecule library is a phage display library.

A<sup>3</sup> 92(New). A compound comprising a target cell specific portion and a directly or indirectly cytotoxic portion, wherein the target cell specific portion comprises an antibody-like molecule having a specificity for T<sub>ck</sub> cells.

93(New). A compound according to claim 92 wherein the antibody-like molecule is selected from the group of molecules consisting of Fab molecules, F(ab<sup>1</sup>)<sub>2</sub> molecules, Fv molecules, disulphide-linked Fv molecules, single chain Fv (scFv) molecules and single domain antibodies (dAbs).

94(New). A compound according to claim 93 wherein said antibody-like molecule is humanized.

95(New). A compound according to any one of claims 92-94 wherein the cytotoxic portion is a directly cytotoxic portion

selected from the group consisting of radionuclides, ricin, ribonuclease, deoxyribonuclease, and *Pseudomonas* exotoxin A.

96(New). A compound according to any one of claims 92-94 wherein the cytotoxic portion is indirectly cytotoxic.

97(New). A compound according to any one of claims 92-94 wherein the cytotoxic portion is capable of inducing apoptosis of the target cells.

98(New). A compound according to any one of claims 92-94 wherein the cytotoxic portion is an enzyme.

99(New). A compound according to claim 97 wherein the cytotoxic portion is an enzyme.

A 100(New). A compound according to any one of claims 92-94 wherein the target cell specific portion and the cytotoxic portion are fused.

101(New). A compound according to claim 100 wherein the target cell specific portion and the cytotoxic portion are separated by a linker sequence.

102(New). A compound according to any one of claims 92-94 having a nucleic acid molecule encoding.

103(New). A compound according claim 101 having a nucleic acid molecule encoding.

104(New). A compound according to any one of claims 92-94 wherein said nucleic acid molecule is included in a vector.

105(New). A compound according to claim 103 wherein said nucleic acid molecule is included in a vector.

106(New). A compound according to claim 104 wherein said vector is included in a host cell line.

107(New). A compound according to claim 105 wherein said vector is included in a host cell line.

108(New). A compound according to claim 82 for use in the treatment of a chronic inflammatory disease.

109(New). A preparation of T-cell enriched cells wherein the cells are from tissue from a site of inflammation in a patient suffering from a chronic inflammatory disease.

110(New). A preparation of cells according to claim 109 wherein the chronic inflammatory disease is rheumatoid arthritis.

*A3  
Concl* 111(New). A preparation of cells according to claim 109 wherein the tissue is from the synovium.

112(New). A preparation of cells according to claim 110 wherein the tissue is from the synovium.

113(New). A preparation of cells according to any one of claims 109-112 wherein the T-cell enriched cells are CD3+-enriched cells.

114(New). A preparation of cells according to any one of claims 109-112 wherein the T-cell enriched cells are non-adherent cells.

---

#### REMARKS

In accordance with the above amendments, the present application is claiming priority as a continuation of the